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ORIGINAL RESEARCH

Sex-Specific Associations of Obstructive Sleep Apnea Risk With Patient Characteristics and Functional Outcomes After Acute Myocardial Infarction: Evidence From the VIRGO Study

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BACKGROUND: Though associations between obstructive sleep apnea (OSA) and cardiovascular outcomes are well described, limited data exist regarding the impact of OSA on sex-specific outcomes after acute myocardial infarction (AMI).

METHODS AND RESULTS: The VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study enrolled 3572 adults aged 18 to 55 years with AMI from the United States and Spain during 2008 to 2012. We included patients for whom the Berlin Questionnaire for OSA was scored at the time of AMI admission (3141; 2105 women, 1036 men). We examined the sex-specific association between baseline OSA risk with functional outcomes including health status and depressive symptoms at 1 and 12 months after AMI. Among both groups, 49% of patients were at high risk for OSA (1040 women; 509 men), but only 4.7% (148) of patients had a diagnosed history of OSA. Though patients with a high OSA risk reported worse physical and mental health status and depression than low-risk patients in both sexes, the difference in these functional outcomes was wider in women than men. Moreover, women with a high OSA risk had worse health status, depression, and quality of life than high-risk men, both at baseline and at 1 and 12 months after AMI.

CONCLUSIONS: Young women with a high OSA risk have poorer health status and more depressive symptoms than men at the time of AMI, which may place them at higher risk of poorer health outcomes over the year following the AMI. Further, the majority of patients at high risk of OSA are undiagnosed at the time of presentation of AMI.

Key Words: acute myocardial infarction ■ Berlin Questionnaire ■ obstructive sleep apnea ■ sex differences

Obstructive sleep apnea (OSA) is often underdiagnosed in patients with acute myocardial infarction (AMI)[1] and is reported to occur in up to 50% of them.[1,2] Sex-specific prevalence of OSA has male preponderance with a ratio of 8:1 in referral populations in sleep centers.[3] However, the sex gap is narrower (2:1) in community-based settings, suggesting that OSA is significantly underdiagnosed among women.[4] Women are less likely to present with the classic symptoms of OSA and more likely to endorse fatigue and depression and are shunted down alternative diagnostic pathways.[5–7] This is important as patients with OSA have been found to have worse cardiovascular outcomes in the setting of coronary disease and acute coronary syndromes,[2,8–10] and there may be sex-based differences in these associations.[11,12] Some studies suggest

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CLINICAL PERSPECTIVE

What Is New?

- Our study finds that young women who present with acute myocardial infarction (AMI) and have high baseline risk of obstructive sleep apnea (OSA) are frequently undiagnosed with OSA.
- Young women with AMI and high baseline risk of OSA have poorer health status and more depressive symptoms than men, which places them at higher risk of poorer health outcomes over the year following the AMI.

What Are the Clinical Implications?

- Our findings suggest a role for incorporating evaluation of OSA risk with the Berlin Questionnaire in the management of AMI, which will further enhance awareness, diagnosis with confirmatory polysomnography, and treatment of OSA and potentially improve clinical outcomes and recovery after AMI.

Nonstandard Abbreviations and Acronyms

MCS	mental component score
PCS	physical component score
PHQ	Patient Health Questionnaire
SAQ	Seattle Angina Questionnaire
SAQ-QoL	Seattle Angina Questionnaire–Quality of Life
SF-12	Short Form-12
VIRGO	Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients

that OSA is associated with increased hypertension, left ventricular hypertrophy, incident heart failure, and death among women more than men, whereas others dispute these findings.[13,14] Randomized controlled trials conducted in patients with acute coronary syndrome[15] or prior cardiovascular disease showed no impact of prevalence or treatment of OSA on hard clinical end points like repeat myocardial infarction, revascularization, stroke or mortality, but <20% of study subjects were women.[16,17]

Further, limited data exist regarding the impact of OSA on sex-specific outcomes after AMI. This is particularly important for young patients with AMI, among whom women have significantly worse outcomes compared with men,[18] despite adjusting for baseline sociodemographic and clinical variables.[19,20] It is possible that sex-related differences in OSA might explain, at least in part, differences in outcomes after AMI.

Polysomnography is the gold standard test for diagnosis of OSA but is inconvenient, time consuming, and expensive. As such, the majority of people with moderate to severe sleep-disordered breathing remain undiagnosed[3] and thus untreated. In the absence of polysomnography, validated screening questionnaires that incorporate common symptoms of OSA (eg, Berlin Questionnaire) are useful in stratifying high- and low-risk patients for sleep-disordered breathing[21–23] and have been endorsed by the US Preventive Services Task Force.[24] Although the Berlin Questionnaire may not be as precise or accurate as polysomnography, it is cost effective and administered quickly, and is best used as a screening tool to determine whether additional tests should be conducted to definitively diagnose sleep apnea.

As such, we used data from the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study (IMJOVEN in Spain), which was specifically designed to address questions regarding the care of young women with AMI in a large geographically diverse patient sample.[25] Our key aim was to examine whether there are sex differences in the association between baseline risk of OSA (measured with the Berlin Questionnaire) and functional outcomes among young and middle-aged patients with AMI. Our findings would help lay the groundwork for incorporating OSA risk evaluation in the management of AMI that will further enhance awareness, diagnosis, and treatment of OSA.

METHODS

Study Population

The authors will make their data, analytic methods, and study materials available to other researchers on reasonable request. The VIRGO study is the largest prospective observational study of young and middle-aged women and men with AMI and was designed to examine sex differences in the presentation, treatment, and outcomes of young and middle-aged patients with AMI. Details on the study design and methodology have been previously reported.[25] In brief, young and middle-aged patients with AMI were enrolled from 103 hospitals in the United States and 24 hospitals in Spain between August 2008 and January 2012 using a 2:1 female-to-male enrollment ratio. A strategy of enrolling all women and 1 of every 6 eligible men (proportion of men:women in this group is 3:1) was used in order to achieve enrollment targets. After the screening algorithm confirmed that an eligible male patient jad been entered into the database, the software program indicated whether that patient was to be enrolled based on random selection. Site coordinators were not allowed to select male participants based on convenience.

Strict adherence to the selection protocol for the comparison group of men was required and monitored by the Yale Operations Committee based on a weekly review of electronic logs by the Operations Committee. Eligible patients were between 18 and 55 years old, met AMI criteria, and presented or transferred to an enrolling institution within the first 24 hours of hospital presentation. AMI criteria included (1) an increase in cardiac biomarkers (troponin I or T or creatine kinase-MB) with at least 1 value >99th percentile of the upper reference limit within 24 hours of admission and (2) supporting evidence of myocardial ischemia, including symptoms of ischemia, ECG changes indicative of new ischemia (ST-segment changes, left bundle-branch block, or the development of pathological Q waves), or other evidence of myocardial necrosis on imaging. Patients who developed elevated cardiac markers as a complication of elective coronary revascularization were not eligible for inclusion in this study. Of the 5585 patients who met eligibility criteria, 3572 patients were enrolled in VIRGO. Of these, we included 3141 patients (2105 women and 1036 men) from the United States and Spain, for whom the Berlin Questionnaire for OSA was scored, in this study. Enrolled and non-enrolled patients had similar demographic characteristics. Institutional review board approval was obtained at each participating center, and all patients provided written informed consent to participate.

Data Collection and Variables

Information on patient demographics, socioeconomic status, health care access, psychosocial risk factors, and symptoms was self-reported by the patient. Data on medical history, comorbidities, time to presentation, and clinical presentation were largely derived from the medical chart; however, in some cases, information from both the medical chart and patient interviews was combined to ensure variable completeness. Trained personnel conducted interviews and reviewed medical charts during the index AMI admission for the following: (1) sociodemographic factors including age (categorized as 18–40 years, 40–55 years), self-identified race (Black, White, others including Asian, American Indian, and Pacific Islander), Hispanic origin, socioeconomic status, and marital status; and (2) medical history including prior coronary disease (AMI, percutaneous coronary intervention, or coronary artery bypass graft), presenting symptoms (typical/atypical chest pain and no symptoms), cardiac risk factors (diabetes, hypertension, dyslipidemia, obesity defined as body mass index [BMI] ≥30 kg/m^2, and smoking status in past 30 days), hemodynamic instability (ventricular tachycardia/fibrillation, blood pressure <90 mm Hg), and the presence of a prehospital ECG. In VIRGO, mortality events were ascertained through interviews with family members and verified with death certificates, hospital records, or obituaries. Health status was ascertained by phone interviews.

Defining High Risk for OSA

We used the Berlin Questionnaire to assess the risk of OSA among patients enrolled in VIRGO.[21] The Berlin Questionnaire reliably identifies middle-aged patients who are at high risk for OSA.[21,22,26] It consists of 10 questions regarding snoring, breathing cessation, and symptoms of excessive daytime sleepiness. Information on height and weight were also incorporated into the assessment of the high or low risk of OSA. In contrast to other screening questionnaires (eg, Sleep Apnea Clinical Score, STOP-BANG) the score does not include sex as a predictor variable.[27,28]

The scoring was based on 3 categories: snoring and cessation of breathing (category 1; 5 questions), symptoms of excessive daytime sleepiness (category 2; 4 questions), and BMI and hypertension (category 3; 1 question, as well as information on height and weight). The predetermination of high risk and low risk for OSA was based on responses to the 3 symptom categories. In category 1, high risk was defined as persistent symptoms (>3–4 times/week) in 2 or more questions regarding their snoring. In category 2, high risk was defined as persistent (>3 to 4 times/week) wake-time sleepiness, drowsy driving, or both. In category 3, high risk was defined as a history of high blood pressure or a BMI >30 kg/m^2. To be considered at high risk for OSA, a patient had to qualify for at least 2 symptom categories. Those who denied having persistent symptoms or who qualified for only 1 symptom category were placed in the lower risk group.

Functional Outcomes

Functional outcomes after AMI included health status and depressive symptoms at 1 and 12 months. Generic health status was evaluated using the Short Form-12 (SF-12) physical and mental component scores (PCS and MCS) administered during the index hospitalization and at 1 and 12 months post-AMI. The SF-12 has been demonstrated to be both a valid and reliable instrument and is the most widely used generic health status instrument to quantify patients' mental and physical functional status.[29] Scores for the PCS and MCS range from 0 to 100, with lower numbers indicating poorer health status. On both, a score of 50 reflects the population mean, and 10 points reflects 1 SD from the mean.

Disease-specific health status was evaluated using the Seattle Angina Questionnaire (SAQ), a 19-item self-administered questionnaire that measures 5 dimensions of coronary artery disease.[30] This measure has been shown to be both valid and reliable in patients

with AMI and has been used extensively in cardiovascular research.[31,32] For this study, we focused on the quality-of-life component (SAQ-QoL), which ranges from 0 to 100, with lower numbers indicating poorer QoL.

Finally, depressive symptoms were assessed using the 9-item Patient Health Questionnaire (PHQ-9).[33,34] Scores range from 0 to 27; higher scores represent greater depressive symptomatology, and a score of ≥10 is suggestive of moderate depressive symptoms.

Statistical Analysis

We compared patient demographics and other baseline characteristics between high and low OSA risk groups, stratified by sex. Specifically, we generated frequencies and percentages to describe categorical variables and used the chi-square test to explore their association with OSA risk. For continuous variables, we calculated the median and interquartile range and tested their association with OSA risk using the Wilcoxon–Mann–Whitney test or the Student *t* test.

Functional outcomes included health status and presence of depression. Unadjusted associations between sleep apnea risk and 1 and 12 months after AMI were evaluated visually by plotting mean health status over time and statistically by using analysis of covariance to control for the baseline SF-12, SAQ-QoL, and PHQ-9 scores. To assess the sex-specific relationship between OSA risk and functional outcomes at 12 months, we used a linear regression model to evaluate differences in SF-12 PCS/MCS, SAQ-QoL, and PHQ-9 scores between OSA risk groups, while adjusting for sex, OSA risk, and the interaction between the two. Potential covariates for multivariable analyses were selected using a combination of clinical and statistical judgment. These included patient demographic data (age, race, BMI, marital status, education, and insurance status), medical history (hypertension, diabetes, previous coronary disease, angina, congestive heart failure, hypercholesterolemia, previous stroke/transient ischemic attack, renal dysfunction, chronic lung disease, smoking status, clinical presentation (GRACE [Global Registry of Acute Coronary Events]) score, presence of ST-segment–elevation myocardial infarction and hemodynamic instability at presentation). Baseline scores for the health status measure being analyzed were included in the models in order to examine the effect of OSA risk on 12-month health status independent of differences in baseline scores. A backwards elimination strategy was used to identify the most parsimonious model for each outcome. The model that minimized the Schwarz Bayesian information criterion was selected as the final model. OSA risk, sex, the interaction between sex and OSA risk, age, BMI, history of hypertension, and baseline scores were all forced in the model regardless of significance. We used the Tukey–Kramer method to adjust for multiple comparisons. Statistical significance was determined using the cutoff of $P<0.05$. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Of the 3501 eligible patients from the United States and Spain, there were 3141 (90%) for which the Berlin Questionnaire for OSA was scored. Of the 3141, 67% (n=2105) were women, and 33% (n=1036) were men. Both groups had 49% of patients who qualified as high risk for OSA as per the Berlin Questionnaire (n=1040 women; n=509 men). Only 4.7% (n=148, 96 women, 52 men) of these patients had a diagnosed history of OSA.

Baseline Characteristics

The baseline characteristics of patients with AMI at high and low risk for sleep apnea are further stratified by sex, as shown in Table 1. The median age and race distribution was similar for patients with high risk and low risk of OSA among both women and men. Overall, women had a higher median BMI than men (30 versus 29 kg/m^2), and, as expected, higher BMI was significantly associated with a high risk of OSA among both women and men. Although patients with high risk of OSA were significantly more likely to have hypertension, diabetes, previous cardiovascular disease, angina, and hypercholesterolemia than those with low risk of OSA in both sexes, the differences for congestive heart failure, renal dysfunction, and prior stroke or transient ischemic attack were significant only in women. Notably, patients with high risk of OSA were less likely to present with hemodynamic instability, ST-segment–elevation AMI, or with ejection fraction <40%. Women with a high risk of OSA were more likely to be current smokers; however, the frequency of alcohol abuse was similar for patients with high risk and low risk of OSA among both women and men.

Functional Outcomes

The Figure demonstrates the baseline, 1-month, and 12-month functional outcomes of patients with AMI and high and low OSA risk, stratified by sex. The 1- and 12-month scores are adjusted for baseline health status. Therefore, differences between OSA risk groups represent the absolute differences in 1- or 12-month health status that remain after adjustment for differences in baseline health status. At baseline during the

Table 1. Baseline Characteristics of Young Adults With AMI Stratified by OSA Risk and Sex

Characteristic	Women			Men		
	High risk	Low risk		High risk	Low risk	
	n=1040	n=1065		n=509	n=527	
	n (%)	n (%)	*P* value	n (%)	n (%)	*P* value
Age, y						
Median (IQR)	48 (44–52)	48 (44–52)	0.539	48 (43–52)	48 (44–52)	0.70
BMI, kg/m^2						
Median (IQR)	33 (28–38)	28 (24–33)	<0.001	31 (28–35)	28 (26–31)	<0.01
Race						
White	797 (76.6)	816 (76.6)	0.761	433 (85.1)	436 (82.7)	0.33
Black	194 (18.7)	189 (17.7)		48 (9.4)	48 (9.1)	
Other*	49 (4.7)	56 (5.3)		28 (5.5)	41 (7.8)	
Married						
Yes	490 (47.1)	551 (51.7)	0.036	300 (58.9)	307 (58.3)	0.91
Education						
Less than high school	49 (4.7)	73 (6.9)	<0.001	13 (2.6)	30 (5.7)	0.04
Some high school	460 (44.2)	375 (35.2)		209 (41.1)	210 (39.8)	
More than high school	516 (49.6)	596 (56.0)		275 (54.0)	275 (52.2)	
Unemployed	489 (47.0)	402 (37.7)	<0.001	154 (30.3)	115 (21.8)	<0.01
No health insurance	232 (22.3)	160 (15.0)	<0.001	114 (22.4)	92 (17.5)	0.05
Hypertension	823 (79.1)	508 (47.7)	<0.001	396 (77.8)	245 (46.5)	<0.01
Diabetes	395 (38.0)	270 (25.4)	<0.001	112 (22.0)	89 (16.9)	0.04
Previous cardiovascular disease	250 (24.0)	136 (12.8)	<0.001	128 (25.1)	74 (14.0)	<0.01
Angina	330 (31.7)	244 (22.9)	<0.001	157 (30.8)	108 (20.5)	<0.01
Congestive heart failure	60 (5.8)	38 (3.6)	0.017	10 (2.0)	10 (1.9)	0.94
Hypercholesterolemia	745 (71.6)	597 (56.1)	<0.001	388 (76.2)	336 (63.8)	<0.01
Obesity (BMI≥30)	676 (65.0)	385 (36.2)	<0.001	305 (59.9)	155 (29.4)	<0.01
Previous stroke/transient ischemic attack	60 (5.8)	41 (3.8)	0.039	12 (2.4)	12 (2.3)	0.93
Renal dysfunction	132 (12.7)	103 (9.7)	0.031	41 (8.1)	39 (7.4)	0.71
Chronic lung disease	168 (16.2)	94 (8.8)	<0.001	37 (7.3)	19 (3.6)	<0.01
Family history of cardiac disease	797 (76.6)	726 (68.2)	<0.001	379 (74.5)	359 (68.1)	0.03
Smoking history						
Never smoked	246 (23.7)	346 (32.5)	<0.001	123 (24.2)	150 (28.5)	0.27
Ever smoked	174 (16.7)	173 (16.2)		107 (21.0)	100 (19.0)	
Current smoker	620 (59.6)	546 (51.3)		278 (54.6)	276 (52.4)	
Alcohol abuse	51 (4.9)	39 (3.7)	0.159	51 (10.0)	57 (10.8)	0.66
ST-segment–elevation myocardial infarction	482 (46.3)	533 (50.0)	0.089	288 (56.6)	321 (60.9)	0.16
Global Registry of Acute Coronary Events score						
Median (IQR)	75 (63–88)	74 (63–87)	0.325	74 (61–86)	72 (59–84)	0.13
Left ventricular ejection fraction <40	91 (8.8)	116 (10.9)	0.104	42 (8.3)	67 (12.7)	0.03
Peak troponin						
Median (IQR)	6 (1–23)	6 (2–23)	0.49	11 (2–36)	9 (2–41)	0.78
Hemodynamic instability at presentation	71 (6.8)	110 (10.3)	0.004	30 (5.9)	50 (9.5)	0.03

Percentages may not add up to 100% due to missing values. AMI indicates acute myocardial infarction; BMI, body mass index; IQR, interquartile range; and OSA, obstructive sleep apnea.

*Other includes Asian, American Indian, Pacific Islander.

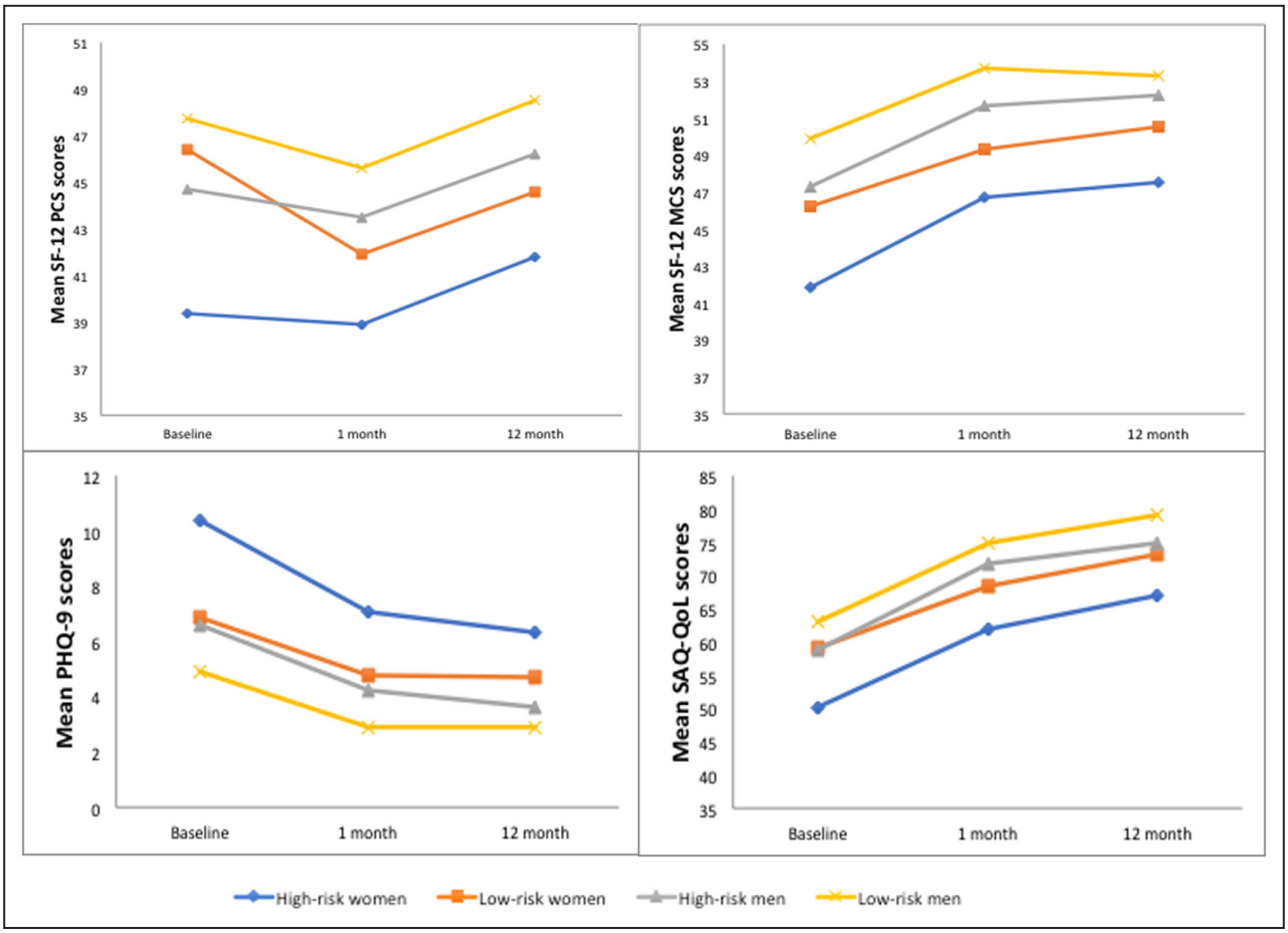

Figure. Mean health status and depression score trajectories at baseline, 1 month, and 12 months after AMI.
AMI indicates acute myocardial infarction; MCS, mental component score; PCS, physical component score; PHQ-9, Patient Health Questionnaire-9; SAQ-QoL, Seattle Angina Questionnaire-Quality of Life; SF-12, Short Form-12; and SF-22, Short Form-22.

initial hospitalization, women and men with a high risk of OSA reported lower physical health status as measured by SF-12 PCS and MCS scores, worse depression as measured by PHQ-9 score and lower QoL as measured by the SAQ-QoL. These differences in health status and depression scores persisted at 1 and 12 months after AMI for both sexes, but differences in mental health status as per the MCS persisted only among women. Although mean health status and depression scores improved in all patients over the 12 months of follow-up regardless of OSA risk, patients with a high risk of OSA (particularly high-risk women) reported poorer health status on the SF-12 and SAQ and more depressive symptoms as per the PHQ-9 at all time points than their counterparts with low risk. Crude mortality at 12 months was very low in this cohort of young patients (~2% overall) and did not differ by OSA risk.

Table 2 shows the association of sex, OSA risk, and their interaction with the magnitude of the difference of scores obtained by high- and low-risk patients on different questionnaires for functional outcomes. There were sex differences in the association between OSA risk and all baseline outcomes, wherein the difference in outcomes between high- and low-risk patients was greater in magnitude among women compared with men. The interaction between OSA risk and sex was significant in all other outcomes except 12-month PCS and SAQ. No significant difference between high- and low-risk patients was found among men with respect to 12-month MCS and PHQ-9.

In risk-adjusted models (Table 3) further adjusting for baseline sociodemographic and clinical variables, we found the interaction between sex and high risk of OSA to be significant in the model for PHQ-9 scores at 12 months (P=0.03), suggesting that the difference in depressive symptomatology between high- and low-risk patients was specific to women.

DISCUSSION

In this multicenter, prospective cohort study, we found that almost half of young and middle-aged adults with AMI qualify as having a high risk of OSA, but only ~5%

Table 2. Interaction Between Sex and OSA Risk for Functional Outcomes*

Outcome by sex	Baseline				12 Month†			
	Mean (SE)		Difference in outcome between high- and low-risk groups‡		Mean (SE)		Difference in outcome between high- and low-risk groups‡	
	High risk	Low risk	Mean (95% CI)	*P* value	High risk	Low risk	Mean (95% CI)	*P* value§
Physical functional status (Short Form-12 physical component score)								
Female	39.4 (0.4)	46.4 (0.4)	−7.0 (−8.3 to −5.6)	<0.001	42.3 (0.4)	45.1 (0.4)	−2.8 (−4.2 to −1.4)	0.53
Male	44.7 (0.5)	47.7 (0.5)	−3.0 (−4.9 to −1.1)		45.2 (0.5)	47.4 (0.5)	−2.2 (−4.1 to −0.3)	
Mental functional status (Short Form-12 mental component score)								
Female	41.8 (0.4)	46.2 (0.4)	−4.4 (−5.8 to −3.1)	0.04	47.9 (0.4)	50.9 (0.3)	−3.0 (−4.3 to −1.7)	0.02
Male	47.3 (0.6)	49.9 (0.5)	−2.5 (−4.5 to −0.5)		51.5 (0.5)	52.5 (0.5)	−1.1 (−2.9 to 0.7)	
Depressive symptomatology (Patient Health Questionnaire-9)								
Female	10.4 (0.2)	6.9 (0.2)	3.6 (2.9 to 4.3)	<0.001	6.0 (0.2)	4.3 (0.2)	1.7 (1.1 to 2.3)	0.01
Male	6.6 (0.3)	4.9 (0.3)	1.7 (0.7 to 2.6)		4.2 (0.2)	3.6 (0.2)	0.7 (−0.2 to 1.5)	
Disease-related quality of life (Seattle Angina Questionnaire-Quality of Life)								
Female	50.2 (0.7)	59.1 (0.7)	−8.9 (−11.6 to −6.3)	0.01	67.6 (0.7)	73.8 (0.7)	−6.2 (−8.8 to −3.5)	0.23
Male	58.8 (1.0)	63.0 (1.0)	−4.2 (−8.0 to −0.5)		73.9 (1.0)	77.9 (1.0)	−4.0 (−7.8 to −0.2)	

OSA indicates obstructive sleep apnea.
*Multivariable linear regression model where the predictor variables included OSA risk, sex, and the interaction between the 2.
†Adjusted for baseline measurement.
‡With adjustment for multiple comparisons using the Tukey–Kramer method.
§*P* value of the OSA risk-sex interaction term.

had a prior diagnosis of OSA. There were significant sex-based differences in patients with AMI who qualified as high-risk for OSA. Women with a high risk of OSA had a higher burden of comorbidities and were more likely to be smokers. Patients with a high risk of OSA reported lower general health status, and median scores at baseline and at 1 and 12 months were worse for women for all functional outcomes, including physical and mental health status and depression. High OSA risk remained an statistically significant predictor of worse physical functional status and quality-of-life at 12 months in adjusted models. The interaction between patient sex and OSA risk was significant when examining association with all functional outcomes at baseline, suggesting that the difference in outcomes between high- and low-risk patients was of greater magnitude in women than men. This interaction remained significant for depressive symptoms and mental health status even at 12 months. Collectively, our results suggest that young women with high risk of OSA have poorer health status and more depressive symptoms than men at the time of AMI, which may place them at higher risk of poorer health outcomes over the year following the AMI.

Table 3. Adjusted 12-Month Outcomes by Sex and OSA Risk

Outcome by sex*	Mean (SE)		Difference in outcome between high- and low-risk groups†	
	High risk	Low risk	Mean (95% CI)	*P* value‡
Physical functional status (Short Form-12 physical component score)				
Female	35.0 (0.8)	37.4 (0.8)	−2.4 (−3.8 to −1.0)	0.76
Male	37.4 (0.9)	39.5 (0.9)	−2.1 (−4.0 to −0.2)	
Mental functional status (Short Form-12 mental component score)				
Female	47.0 (0.5)	49.9 (0.5)	−2.8 (−4.2 to −1.5)	0.07
Male	50.0 (0.6)	51.3 (0.6)	−1.3 (−3.2 to 0.6)	
Depressive symptomatology (Patient Health Questionnaire-9)				
Female	7.7 (0.3)	6.1 (0.3)	1.6 (1.0 to 2.2)	0.03
Male	6.1 (0.3)	5.4 (0.3)	0.8 (−0.1 to 1.6)	
Disease-related quality of life (Seattle Angina Questionnaire-Quality of Life)				
Female	59.8 (1.5)	66.1 (1.5)	−6.2 (−9.1 to −3.4)	0.48
Male	65.2 (1.7)	70.2 (1.6)	−5.0 (−8.8 to −1.1)	

Multivariable linear regression model where the predictor variables included OSA risk, sex, the interaction between the 2, and select baseline risk factors. OSA indicates obstructive sleep apnea.
*Adjusted for baseline measurement.
†With adjustment for multiple comparisons using the Tukey–Kramer method.
‡*P* value of the OSA risk-sex interaction term.

This study extends the previous literature in several important ways. First, this is one of the largest and most geographically diverse studies describing sex differences in risk for OSA in young patients with AMI. Second, most prior studies of OSA, whether observational or randomized, have included >80% men.[16,17] In contrast, our study enrolled women and men in a 2:1 ratio, enabling a robust analysis of OSA risk in women, although we were not able to have diagnostic confirmation of OSA. Third, no previous study has provided such a comprehensive evaluation of the association of OSA risk with physical and mental health status outcomes in patients with AMI. Most of the existing

literature has focused on outcomes such as mortality that may not comprehensively describe the association of OSA with outcomes after AMI, particularly from the patient's perspective. Fourth, we were able to demonstrate an interaction of female sex with OSA risk for worse health status outcomes and had, with the male control subjects, the ability to determine the differences in magnitude across various time points after AMI. Finally, we were able to show that the differences in several functional outcomes remained wider for women than men, even after adjustment for a range of important confounders over the year after AMI.

The low percentage of patients diagnosed with OSA among the group at high risk for OSA suggests a very high burden of potentially undiagnosed OSA among patients with AMI, even though they were not definitively diagnosed using polysomnography. Our findings are in concordance with prior studies that found similarly elevated prevalence of OSA in patients hospitalized with AMI ranging from 40% to 70%[35,36] and high rates of underdiagnosis.[1,37] These rates are much higher than those reported to be <10% from the general population, likely due to risk factors common to both OSA and coronary artery disease. It has been reported that 75% to 80% of OSA cases that could benefit from treatment in the United States remain undiagnosed.[38] The association between OSA and cardiovascular diseases has received increasing recognition in recent years. In fact, the European guidelines on cardiovascular disease prevention in clinical practice recognize OSA as a disease with increased risk for cardiovascular disease and recommend screening for and treating OSA in patients with chronic coronary artery disease and hypertension.[39] It should be noted, however, that randomized controlled trials in recent years have not borne out the benefit of treatment of OSA in these populations with acute coronary syndrome or established cardiovascular disease on hard clinical end points.[15–17] All of these trials enrolled <20% women. The American Academy of Sleep Medicine advocates for physicians to ask all adult patients about signs and symptoms of OSA as part of a routine health maintenance evaluation.[40] The American specialty associations for cardiovascular disease, however, do not make any recommendations regarding screening for OSA.

Several comorbidities such as hypertension, diabetes, previous cardiovascular disease, angina, and hypercholesterolemia were associated with a high risk of OSA in both women and men. The associations may be due in part to risk factors common to all these conditions; they may also reflect a role of OSA in the pathogenesis of these conditions.[38] We also found an association of smoking, stroke, transient ischemic attack, and congestive heart failure with a high risk of OSA, all conditions previously reported as predictors of OSA, although the reasons for the sex-specific association in our study are less clear. Interestingly, we found that patients with high risk of OSA presented with less severe AMI as noted by less frequent presentation of hemodynamic instability or ST-segment–elevation myocardial infarction or ejection fraction <40%. This phenomenon of ischemic preconditioning in patients with OSA has previously been described by Shah et al suggesting a possible cardioprotective effect of OSA in the acute phase of myocardial infarction.[41]

Our most notable finding is that women with a high risk of OSA score worse than men for all functional outcomes, including depression and health status, that place them at higher risk of poorer health outcomes over the year following the AMI. We have previously published our findings demonstrating higher rates of depressive symptoms[42] and worse health status[43] among women with AMI compared with men up to 1 year post AMI. The present analyses provide novel information that may partially explain the persistent finding of worse outcomes after AMI among young women compared with men. Young women have been consistently shown to have worse outcomes, including mortality, compared with men.[18] The mechanism underlying this disparity has not been clearly explained despite adjustment for sociodemographic and clinical variables in several studies.[18–20] We demonstrate that women with a high risk of OSA have a different phenotype than men with a high risk of OSA and have a much worse health status profile at the time of their AMI that persists for the year after AMI. Moreover, the impact of high OSA risk on functional outcomes is stronger on women than men, as seen by the significant interaction between sex and OSA for all functional outcomes. As the majority of OSA goes undiagnosed and affects the health status of women disproportionately than men, it is plausible that early diagnosis and treatment of OSA in these patients may help narrow the sex gap in outcomes after AMI and should be the focus of future investigations. Further, several studies have described a complex relationship between depression and OSA in terms of diagnosis, clinical presentation and treatment.[44] Up to 20% of patients presenting with a diagnosed depressive disorder may also have OSA and vice versa. It has also been shown that OSA treatment with continuous positive airway pressure helps lower depression scores in these patients.[45] As such, increased awareness of this relationship would help raise the diagnostic accuracy and treatment outcome for both of these disorders, particularly in women.

Limitations

Our study has several limitations. First, we used the Berlin score as a proxy for OSA. As such, we could have over- or underestimated the prevalence of OSA in our study. However, we have used the term high-risk of

OSA throughout the article to clarify the precise variable that we measured. Further, despite availability of other similar questionnaires, we used the Berlin score as it is the most validated and is less likely to underdiagnose OSA in women as compared with the other scores including SACS and STOP-BANG. In fact, we observed similar prevalence of high risk of OSA in women and men, suggesting that the Berlin Questionnaire has no sex-based bias in measuring risk. Further, any misclassification of the exposure would tend to bias toward the null hypothesis and not explain our findings as pertaining to difference in functional outcomes between women and men. Second, there was a shift in the interview mode from in-person interviews at baseline to telephone interviews during follow-up. Although this change in interview mode may have influenced patient responses to questions, trained interviewers administered all interviews, and interview modes were consistent across all patients at each time point. Any changes in patients' responses resulting from interview mode should be the same for all patients regardless of the risk of OSA. Third, performing a longitudinal study with patient interviews requires patient consent and participation. As occurs in these studies, some patients were lost to follow-up, and some patients did not respond to requests for a follow-up interview. The percentages, however, were similar for women and men, and this does not appear to have imposed a bias. Fourth, because this was an observational study, the differences between women and men in health status may be attributable to residual confounding. However, our detailed data collection allowed us to adjust for an extensive range of patient-level factors that are typically not included in sex-based research. Fifth, because patients were required to be healthy at baseline to participate, the VIRGO cohort was unable to capture those patients who were too ill to be enrolled.

CONCLUSIONS

In conclusion, young women with a high risk of OSA have poorer health status and more depressive symptoms than men at the time of AMI, which may place them at higher risk of poorer health outcomes over the year following the AMI. Further, young patients with AMI have potentially high rates of undiagnosed OSA. This information may lay the foundation for future efforts to incorporate OSA screening as a routine part of clinical examination for patients with coronary artery disease and can improve detection and treatment of OSA and ultimately outcomes for young women with AMI.

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